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=> s xenon
L9      101295 XENON

=> s hypothermia
L10      57701 HYPOTHERMIA

=> s l9 and l10
L11        107 L9 AND L10

=> s l11 and neonatal
L12         13 L11 AND NEONATAL

=> dup rem l12
PROCESSING COMPLETED FOR L12
L13           9 DUP REM L12 (4 DUPLICATES REMOVED)
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=> d l13 1-9 ibib kwic

L13  ANSWER 1 OF 9  USPATFULL on STN
ACCESSION NUMBER:        2007:120595  USPATFULL Full-text
TITLE:                   Use of xenon with hypothermia for
                         treating neonatal asphyxia
INVENTOR(S):             Franks, Nicholas Peter, Highbury, UNITED KINGDOM
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PATENT ASSIGNEE(S):      PROTEXEON LIMITED, London, UNITED KINGDOM, WC2B 4HN
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                                                 20060323  PCT 371 date

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DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    FAY SHARPE LLP, 1100 SUPERIOR AVENUE, SEVENTH FLOOR,
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NUMBER OF CLAIMS:        45
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      16 Drawing Page(s)
LINE COUNT:              1521
TI     Use of xenon with hypothermia for treating
       neonatal asphyxia
AB      The present invention relates to the use of xenon in the preparation of a
       medicament for the treatment of neonatal asphyxia in a neonatal subject,
       wherein said medicament is for use in combination with hypothermia.
SUMM    The present invention relates to a method of treating neonatal
       asphyxia.
SUMM    Neonatal (or perinatal) asphyxia, also known as
       hypoxia-ischemia (HI), is a condition arising from the inadequate intake
       of oxygen in an infant during labour, delivery, or the immediate
       postnatal period. Neonatal asphyxia remains a major cause of
       chronic neurological morbidity and acute mortality in the newborn
       (Balduini et al, 2000; Vannucci. . .
SUMM    Studies have shown that neonatal asphyxia (hypoxia) for as
       short a time as six minutes can lead to permanent neurological damage.
       Loss of brain tissue. . .
SUMM    About 14.6% of all deaths at birth are caused by neonatal
       asphyxia. In the western world about 0.9% (i.e. 100-130,000) of newborns
       suffer from neonatal asphyxia. About 15-20% die, and of the
       survivors, 25% are severely handicapped due to long-term complications
       such as mental retardation,. . . asphyxia, who seem initially to
       recover without complications, have behavioral problems in childhood,
       which can be traced back to this neonatal insult.
       Neonatal asphyxia meets the criteria for an orphan drug
       indication since it affects less then 5 patients in 10,000 inhabitants,
       and. . .
SUMM    It has been demonstrated in neonatal animal models of HI that
       the mechanisms of cell death involved in this type of brain injury,
       involve a combination. . .
```

SUMM The present invention seeks to provide a method of treating neonatal asphyxia.

SUMM A first aspect of the invention relates to the use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia, wherein said medicament is for use in combination with hypothermia.

SUMM A second aspect of the invention relates to a method of treating neonatal asphyxia in a mammal in need thereof, said method comprising:

SUMM (a) administering a therapeutically effective amount of xenon to the mammal; and

SUMM (b) subjecting the mammal to hypothermia.

SUMM A third aspect of the invention relates to a method of treating neonatal asphyxia in a mammal in need thereof, said method comprising administering a therapeutically effective amount of xenon to the mammal in combination with hypothermia.

SUMM A fourth aspect of the invention relates to the use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia, wherein said treatment comprises administering to a subject simultaneously, sequentially or separately xenon in combination with hypothermia.

SUMM A fifth aspect of the invention relates to the use of xenon, in combination with hypothermia, for the treatment of neonatal asphyxia.

SUMM . . . on an adequate blood supply (Choi and Rothman, 1990). Should the blood supply become interrupted, as is the case in neonatal asphyxia, hypoxic-ischaemic damage to the area downstream will ensue within minutes. Under these conditions of oxygen depletion, cellular metabolism shifts. . .

SUMM . . . appears to be both time-dependent and location-dependent, with the initial necrotic injury being confined to the ipsilateral forebrain in a neonatal rat model of HI, and the delayed apoptotic injury occurring in the thalamus (Northington et al, 2001). This suggests that. . .

SUMM Xenon as a Neuroprotectant

SUMM Xenon is an apolar, inert gas that is a potent NMDA antagonist (Franks et al, 1998). Like other NMDA antagonists, it. . . and in vivo (Homi et al, 2003; Wilhelm et al, 2002). However, unlike many of the other NMDA receptor antagonists, xenon is not neurotoxic (Ma et al, 2002). A further advantage of using xenon as an NMDA antagonist is that the molecule is an inert, volatile gas that can be rapidly eliminated via respiration.

SUMM Xenon has many other favourable properties. Since its first use in surgery (Cullen S C et al, Science 1951; 113:580-582), a. . . 1994; 38:121-125; Goto T et al, Anesthesiology 1997; 86:1273-1278; Marx T et al, Br. J. Anaesth. 1997; 78:326-327). Moreover, as xenon is a small, uncharged atom, it can easily pass through the blood-brain barrier thus producing a rapid onset of action (Nakata et al, 2001). It also has a very low blood: gas partition coefficient lending to fast emergence from xenon anaesthesia (Goto et al, 1997). As well as these advantages, xenon is non-explosive, non-toxic and unreactive (Shichino et al, 2002), and this makes xenon an ideal candidate for use as a neuroprotectant in the neonate.

SUMM Hypothermia as a Neuroprotectant

SUMM Talbot first demonstrated the neuroprotective properties of hypothermia for surgical use in 1941 (Talbot, 1941). Currently, the only routine use of hypothermia is during cardiopulmonary bypass to protect the brain from intra-operative ischaemia. However, there have been several publications demonstrating the therapeutic effect of hypothermia in other models of brain injury. For

example, numerous publications exist showing the beneficial effect of hypothermia in both in vitro (Onitsuka et al, 1998) and in vivo models of neonatal asphyxia (Debillon et al, 2003; Treschera et al, 1997). It has been demonstrated that a direct correlation exists between tissue. . .

SUMM The mechanism by which hypothermia exerts its neuroprotective effect has yet to be elucidated, but many theories have been postulated. Studies have suggested that the mechanisms by which hypothermia is protective are temperature and time-dependent, and may act at more than one point along the cascade of events that. . . a moderate temperature of 31° C. has been shown to be neuroprotective by decreasing cerebral energy metabolism, whereas a mild hypothermia of 34° C. while also neuroprotective, has no effect on energy metabolism and must therefore act via a different mechanism (Yager and Asselin, 1996). Another study by Taylor et al (Taylor et al, 2002) demonstrated that hypothermia instituted after the HI insult was more effective than intra-ischaemic hypothermia, and suggested that this may be due to a decrease of deleterious effects that occur during the recovery period. An example of one such mechanism could be that hypothermia decreases the excitotoxic damage that ensues during reperfusion (Taylor et al, 2002). Many other mechanisms of protection by hypothermia have been suggested, including the reduction of reactive oxygen species (Taylor et al, 2002), a reduction in tissue acidosis (Chopp. . .

SUMM Xenon and Hypothermia in Combination

SUMM As mentioned above, a first aspect of the present invention relates to the use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia in a neonatal subject, wherein said medicament is for use in combination with hypothermia.

SUMM As used herein, the term "hypothermia" refers to subjecting a particular subject (in this case, a neonatal subject) to hypothermic conditions, for example, by lowering the body temperature, preferably by 3-5° C., through passive or active techniques.. .

SUMM As mentioned above, the use of hypothermia in the treatment of neonatal asphyxia has been well documented in the art (see for example, Volpe, 2001; Gunn et al, 2000). However, to date there has been no teaching or suggestion in the art that hypothermia could be use in combination with the administration of xenon. Nor has there been any suggestion that such combination therapy would lead to such a surprising and unexpected enhancement in. . .

SUMM Previous studies by the applicant have revealed that xenon has neuroprotective properties. In particular, WO 01/08692, the contents of which are incorporated herein by reference, relates to the use of xenon as a neuroprotectant and/or as an inhibitor of synaptic plasticity. However, there is no teaching or suggestion in the prior art that xenon would be effective as a neuroprotectant in the context of the presently claimed invention.

SUMM In one preferred embodiment of the invention, the xenon is admixed with a pharmaceutically acceptable diluent, excipient or carrier.

SUMM . . . invention is also applicable to the treatment of animals. In this regard, the invention further relates to the use of xenon in combination with: a veterinarily acceptable diluent, excipient or carrier.

SUMM For veterinary use, the xenon is typically administered in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route. . .

SUMM The xenon may also be administered in combination with

another pharmaceutically active agent. The agent may be any suitable pharmaceutically active agent. . .

SUMM In one preferred embodiment, the xenon is administered in combination with a volatile anesthetic agent, preferably isoflurane, sevoflurane or desflurane.

SUMM The xenon may also be administered in combination with other active ingredients such as L-type calcium channel blockers, N-type calcium channel blockers,. . .

SUMM The xenon may be administered by any suitable delivery mechanism, or two or more suitable delivery mechanisms.

SUMM In one particularly preferred embodiment, the xenon is administered by perfusion. In the context of the present invention, the term "perfusion" refers to the introduction of an oxygen/xenon mixture into, and the removal of carbon dioxide from, a patient using a specialised heart-lung machine. In general terms, the. . . to control the level of oxygen and carbon dioxide. In the context of the present invention, the perfusionist also introduces xenon into the patient's blood. The perfusionist then propels the blood back into the arterial system to provide nutrient blood flow. . .

SUMM In another highly preferred embodiment, the xenon is administered by inhalation. More preferably, the xenon is administered by inhalation of a 70-30% v/v xenon/oxygen mixture.

SUMM More preferably, the xenon is administered in the form of a 20-70% v/v xenon/air mixture.

SUMM In one particularly preferred embodiment, the xenon is administered in the form of a lipid emulsion. The intravenous formulation typically contains a lipid emulsion (such as the. . . Intralipid®20, Intrafat®, Lipofundin®S or Liposyn® emulsions, or one specially formulated to maximise solubility) which sufficiently increases the solubility of the xenon to achieve the desired clinical effect. Further information on lipid emulsions of this sort may be found in G. Kleinberger. . .

SUMM It has been established that appreciable amounts of xenon maybe added to a lipid emulsion. Even by the simplest means, at 20° C. and normal pressure, xenon can be dissolved or dispersed in concentrations of 0.2 to 10 ml or more per ml of emulsion. The concentration. . .

SUMM The lipid emulsions of the present invention may be loaded with gaseous xenon. In general, a device is filled with the emulsion and anaesthetics as gases or vapours passed through sintered glass bubblers. . .

SUMM The lipid emulsions of the present invention may be loaded so that the xenon is at the saturation level. Alternatively, the xenon may be present in lower concentrations, provided, for example, that the administration of the emulsion produces the desired pharmaceutical activity.

SUMM The concentration of xenon employed in the invention may be the minimum concentration required to achieve the desired clinical effect. It is usual for. . .

SUMM Preferably, the xenon is administered simultaneously, in combination, sequentially or separately with hypothermia.

SUMM As used herein, "simultaneously" is used to mean that the xenon is administered concurrently with hypothermia, whereas the term "in combination" is used to mean the xenon is administered, if not simultaneously, then "sequentially" within a timeframe in which the xenon and the hypothermia both exhibit a therapeutic effect, i.e. they are both are available to act therapeutically within the same time-frame. Thus, administration "sequentially" may permit the xenon to be administered within

5 minutes, 10 minutes or a matter of hours before the hypothermia, provided the circulatory half-life of the xenon is such that it is present in a therapeutically effective amount when the neonatal subject is exposed to hypothermic conditions.

SUMM In another preferred embodiment of the invention, the neonate is subjected to hypothermia prior to treatment with xenon .

SUMM In contrast to "in combination" or "sequentially", "separately" is used herein to mean that the gap between administering the xenon and exposing the neonatal subject to hypothermia is significant i.e. the xenon may no longer be present in the bloodstream in a therapeutically effective amount when the neonatal subject is exposed to hypothermic conditions.

SUMM In one preferred embodiment, the xenon is administered sequentially with hypothermia.

SUMM More preferably, the xenon is administered sequentially before the hypothermia.

SUMM In another preferred embodiment, the xenon is administered separately before the hypothermia.

SUMM In one preferred embodiment, the xenon is administered sequentially after the hypothermia.

SUMM In another preferred embodiment, the xenon is administered separately after the hypothermia.

SUMM More preferably, the xenon is administered sequentially or simultaneously with hypothermia, more preferably simultaneously.

SUMM In one preferred embodiment of the invention, the xenon is administered in a therapeutically effective amount.

SUMM In another preferred embodiment, the xenon is administered in a sub-therapeutically effective amount. In other words, the xenon is administered in an amount that would be insufficient to produce the desired therapeutic effect if administered in the absence. . .

SUMM Even more preferably, the combination of xenon and hypothermia has a synergistic effect, i.e., the combination is synergistic.

SUMM In one particularly preferred embodiment, the xenon is administered prior to the hypoxic insult. Thus, in one preferred embodiment, the xenon is administered to the neonate via the mother prior to birth, for example, by administering to the mother prior to or during labour. Preferably, the xenon is administered to the mother for up to about 48 or 24 hours prior to birth, more preferably up to. . .

SUMM Another aspect of the invention relates to a method of treating neonatal asphyxia in a mammal in need thereof, said method comprising:

(a) administering a therapeutically effective amount of xenon to the mother of the mammal prior to and/or during labour; and

(b) subjecting the mammal to hypothermia after birth.

SUMM Preferably, the hypothermia is maintained for a period of at least about 6 hours, more preferably at least about 12 hours, after the. . .

SUMM In one preferred embodiment, the hypothermia is maintained for a period of from about 6 to about 24 hours after the hypoxic-ischemic (HI) insult.

SUMM Preferably, the hypothermia is maintained for a period of at least about 6 hours, more preferably at least about 12 hours, after birth.

SUMM In one preferred embodiment, the hypothermia is maintained

for a period of from about 6 to about 24 hours after birth.

SUMM Hypothermia may be produced passively, by allowing the temperature to drift downwards and not purposefully sustain body temperature. Being poikilothermic, neonates. . .

SUMM A second aspect of the invention relates to a method of treating neonatal asphyxia in a mammal in need thereof, said method comprising:

SUMM (a) administering a therapeutically effective amount of xenon to the mammal; and

SUMM (b) subjecting the mammal to hypothermia, or hypothermic conditions.

SUMM Preferably, the mammal is subjected to conditions of mild hypothermia. As used herein, the term "mild hypothermia " typically refers to a decrease in the core temperature from 37° C. to about 33° C.

SUMM Another aspect of the invention relates to a method of treating neonatal asphyxia in a mammal in need thereof, said method comprising administering a therapeutically effective amount of xenon to the mammal in combination with hypothermia.

Yet another aspect of the invention relates to the use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia, wherein said treatment comprises administering to a subject simultaneously, sequentially or separately xenon in combination with hypothermia.

SUMM A further aspect of the invention relates to the use of xenon , in combination with hypothermia, for the treatment of neonatal asphyxia.

SUMM Using an animal model of HI, neonatal rats were exposed to treatment with xenon and hypothermia independently of each other. Xenon was shown to be neuroprotective against HI in the neonate by reducing the amount of apoptotic cell death, while hypothermia appeared less effective. In combination, xenon and hypothermia were neuroprotective via an anti-apoptotic mechanism (FIG. 17). Their combined effect was found to be synergistic.

SUMM The neonatal rat HI model is very established and has been validated for use in a number of previous studies (Levine, 1960;. . .

SUMM During the hypothermia experiments, the temperature of the rat pups was monitored using a probe that was inserted into the cortex of one. . .

SUMM The anaesthetic gas xenon has been shown to exhibit neuroprotection in several models of adult neuronal injury. Currently, no published data exist to confirm the same neuroprotective effect of xenon in neonates. The results of this study corroborate previous findings that xenon has significant neuroprotective properties and in addition, suggest that this neuroprotection extends to neonatal models of brain injury induced by hypoxia-ischaemia.

SUMM . . . of glutamate receptors is required to sustain ongoing neuronal injury and death in HI, and it is well documented that xenon exerts its analgesic and anaesthetic effect via blockade of these receptors, thus it has been postulated that xenon's neuroprotective properties are as a result of this antagonism. Previously, several other NMDA antagonists have demonstrated neuroprotection in in vitro. . . it is possible that blockade of the glutamate receptor subtype is insufficient to protect against injury, which would imply that xenon exerts its neuroprotective effect through another mechanism.

SUMM In the present study, it has been demonstrated that xenon significantly protects against neonatal HI via an anti-apoptotic mechanism. Both apoptosis and necrosis are important components of neuronal loss after HI injury, but apoptosis appears to be the more important type of cell death in determining neonatal outcome (Taylor et al, 1999). Apoptotic death is often preceded by the activation of many genes, (including transcription factors) which may be either pro-apoptotic or anti-apoptotic. As xenon appears to interfere with apoptotic cell death, it is possible that it may exert its effect on one of these. . . of cytochrome c, Apaf-1 (apoptosis protease-activating factor-1) and caspase-9, and the subsequent activation of caspase-3. It is entirely possible that xenon acts on either one of these pathways, but there is evidence to suggest that apoptotic neurodegeneration induced by HI is. . . pro- and anti-apoptotic proteins, namely by inhibiting the HI-induced bax increase (Engelhard et al, 2003). Thus it is possible that xenon could inhibit apoptosis by downregulating bax. Bcl-2 is an anti-apoptotic protein that acts to decrease the permeability of the mitochondria. . . transient global cerebral ischaemia in gerbils (Engelhard et al, 2003). Therefore, the upregulation of bcl-2 is another potential target for xenon. As xenon is apolar and fat soluble, it is able to distribute itself widely throughout the body. It can penetrate membranes and. . .

SUMM Anti-necrosis by xenon was shown to be statistically significant in the cortex at 48 h, but not in the gyrus (FIG. 16). At all other time groups, xenon was not anti-necrotic. One possible explanation for this is that in accordance with a previous study (Northington et al, 2001),. . . present in the positive controls at 48 h, compared with 16 and 24 h. Although it is not certain how xenon exerts an anti-necrotic effect in the cortex at 48 h, it may be that while xenon is unable to prevent necrosis that occurs before its administration (as in the 16 and 24 h groups), it is. . . Initial necrosis occurs as early as 3 h after the HI insult (Northington et al, 2001) and at this point xenon has not yet been administered. It is therefore unlikely to be able to arrest or reverse a process that has already occurred. However, the secondary necrotic wave occurs at a time at which xenon has been present in the brain for 48 h, and this suggests that the presence of xenon at the advent of necrosis may be able to decrease this type of cell death. Further work must to be. . .

SUMM Previous studies have demonstrated that mild hypothermia of 33° C. is neuroprotective against ischaemic neuronal injury (Busto et al, 1987). Other studies have suggested that this neuroprotection. . .

SUMM . . . h however, significant neuroprotection was achieved in both the cortex and the gyrus, but by different mechanisms. In the cortex, hypothermia is anti-necrotic and in the gyrus, it is anti-apoptotic (FIG. 16). The data in this study do not explain this. . . vulnerability (Northington et al, 2001). In the cortex, the secondary necrotic wave (discussed above) occurs at a time at which hypothermia has already been administered, and this may make it more effective. In the gyrus however, there is no delayed necrosis. . . appears to be the neuroprotective mechanism in this region, and it is possible that the expected anti-apoptotic neuroprotective effect of hypothermia, that is not evident at the earlier time intervals, may be exposed after longer periods.

SUMM The results demonstrated that when used in combination, 20% xenon and 35° C. hypothermia provided an astounding level of neuroprotection. As these values provided no neuroprotection when each agent was used alone, the result. . .

SUMM By way of summary, the present study has shown using an in vivo rat model to show that xenon is neuroprotective in the neonate, and significantly protects against apoptosis induced by

hypoxic-ischaemic injury. The data in this study also suggest that when xenon and hypothermia are used in combination in the same model, they interact synergistically to dramatically decrease apoptotic cell death. Accordingly, this combination may represent an effective treatment to protect against the devastating neurological consequences of neonatal asphyxia.

DRWD FIG. 4 shows the concentration-dependence of xenon neuroprotection (ratio right hemisphere weight/left against xenon concentration).

DRWD FIG. 5 shows the effect of 70% xenon on neurological functions assessed remotely after hypoxic-ischemic (HI) insult.

DRWD FIG. 6 compares the neuroprotective effect (ratio of right hemisphere/left) observed with N.sub.2 and xenon respectively, when xenon is administered 2 hours post HI insult.

DRWD FIG. 7 shows the effect of mild hypothermia on the neuroprotective effect of xenon (LDH release against xenon concentration, % atm).

DRWD FIG. 9 shows a photograph of the purpose-built airtight chambers used for gas delivery. The water bath and closed circuit xenon delivery system are also depicted.

DRWD . . . surgery of n=12 pups. Recovery periods were undertaken in the dam. The interventions used were: sham animals, positive controls, 75% xenon (balance oxygen), 33° C. hypothermia, 20% xenon (25% oxygen, 55% nitrogen), 35° C. hypothermia, and a combination of 35° C. hypothermia and 20% xenon. Unless otherwise indicated, animals were kept at 37° C. and breathed a gas mixture of 25% oxygen balanced with nitrogen.. . .

DRWD FIG. 13 shows that xenon is neuroprotective at 16 h via an anti-apoptotic mechanism. More specifically, FIG. 13 shows graphs for apoptotic and necrotic neuronal death induced by hypoxic-ischaemia, and the effects of 75% xenon and 33° C. hypothermia on such cell death at 16 h in (A) the cortex, and (B) the gyrus. In both brain areas xenon significantly increases the percentage of viable cells as well as decreasing the percentage of apoptotic cells compared to positive control animals. In the cortex, hypothermia decreases the percentage of apoptotic cells, although it does not increase the viable cell count and can therefore not be. . .

DRWD FIG. 14 shows a photomicrograph demonstrating the cortex and gyrus in the sham, positive control and 75% xenon animals at 16 hours. The 75% group is more similar in appearance to the sham group than the positive control group. This confirms the neuroprotective effect of xenon at 16 hours. The gyrus of the control group is distorted in shape due to the increased amount of cell. . .

DRWD FIG. 15 shows that xenon is neuroprotective at 24 h via an anti-apoptotic mechanism. More specifically, FIG. 15 shows graphs for apoptotic and necrotic neuronal death induced by hypoxic-ischaemia, and the effects of 75% xenon and 33° C. hypothermia on such cell death at 24 h in (A) the cortex, and (B) the gyrus. In both brain areas xenon causes a significant increase in the percentage of viable cells due to a decreased necrotic cell count. Results are mean±SD. . .

DRWD FIG. 16 shows that xenon is neuroprotective at 48 h via an anti-apoptotic mechanism More specifically, FIG. 16 shows graphs for apoptotic and necrotic neuronal death induced by hypoxic-ischaemia, and the effects of 75% xenon and 33° C. hypothermia on such cell death at 48 h in (A) the cortex, and (B) the gyrus. Xenon is neuroprotective via an anti-apoptotic mechanism in both the cortex and the gyrus. In addition, xenon has an anti-necrotic effect in the cortex. 33° C. hypothermia

appears to be neuroprotective in both brain areas, but by a different mechanism--it is anti-necrotic in the cortex, and anti-apoptotic. . .

DRWD FIG. 17 shows that a combination of xenon and hypothermia interact synergistically to produce anti-apoptotic neuroprotection. More specifically, FIG. 17 shows graphs for apoptotic and necrotic neuronal death induced by hypoxic-ischaemia, and the effect of a combination of 20% xenon and 35° C. hypothermia on such cell death at 16, 24 and 48 h in (A) the cortex, and (B) the gyrus. No difference was seen when the 20% xenon group and the 35° C. hypothermia group were compared to positive controls, thus at these values there is no neuroprotection. When these values are used in. . .

DETD Neonatal Asphyxia Model

DETD . . . placed in a specially designed area with constant of room temperature (23° C.) and humidity (48%). One hour after surgery, neonatal rats were placed in specially designed chamber with 8% oxygen combined with 0, 20, 40, 60 or 70% Xenon (with nitrogen making up the balance) for 90 min at 37° C. (temperature kept by water bath running outside chambers).. . .

DETD . . . The brain slices on the right are from animals that have suffered the same hypoxia-ischemia but have been breathing 70% xenon during the hypoxic period. These brains look close to normal showing the remarkable neuroprotection afforded by xenon .

DETD The concentration-dependence of xenon neuroprotection (ratio right hemisphere weight/left against xenon concentration) is shown in FIG. 4. In more detail, FIG. 4 shows the ratios of ipsilateral/contralateral hemispheric weight of 14 day rat brain after hypoxia/ischemia with or without various concentrations of xenon at 7 days old. Neuroprotection is evident even at sub-anaesthetic concentrations. Control animals were subjected to carotid ligation but no. . .

DETD The effect of 70% xenon on neurological functions assessed remotely after hypoxic-ischemic (HI) insult is shown in FIG. 5. At postnatal day 7 the right. . .

DETD The neuroprotective effect (ratio of right hemisphere/left) observed with N.sub.2 and xenon respectively is shown in FIG. 6, when xenon is administered 2 hours post HI insult. In more detail, the data show that xenon is effective in providing neuroprotection even if it is administered 2 hours after the end of the hypoxic period. The. . .

DETD The effect of mild hypothermia on the neuroprotective effect of xenon (LDH release against xenon concentration, % atm) is shown in FIG. 7. Modest hypothermia produces a very large and unexpected enhancement in xenon neuroprotection. Cooling by 4 degrees greatly enhances the potency of xenon in blocking LDH release. In more detail, this figure shows the effect of a combination of xenon and hypothermia on oxygen-glucose deprivation (OGD)-induced lactate dehydrogenase (LDH) release. FIG. 7 shows the results of exposing neuronal cultures to 75 minutes OGD in the presence of increasing concentrations of xenon, either at 37° C. (red), or at 33° C. (blue). The ED.sub.50 values for xenon at 37° C. vs xenon at 33° C. were 35.9+/-2.15% and 11.5+/-2.0% (means +/-SEM) respectively. Neuronal injury is expressed as a percentage of the maximal LDH release after 75 minutes of OGD and 6 hours of recovery in the absence of either xenon or hypothermia. Points represent mean values, with error bars indicating standard errors.

DETD . . . of the temperature dependence. The data in red show the effect

of temperature on LDH release in the absence of xenon. The reduction of release as the temperature is reduced is expected but modest. When 12.5% xenon is present, the temperature dependence is very large and unexpected. Hypothermia therefore appears to greatly enhance the neuroprotective effects of xenon . Accordingly, the results suggest that hypothermia and xenon act synergistically as neuroprotectants.

DETD Treatment with Hypothermia

DETD Rat pups underwent 90 minutes of treatment with mild hypothermia (33° C.). One pup was selected at random, and under isoflurane and local anaesthesia, a temperature probe (Mini-Mitter Co. Inc.,. . . C., as measured by the temperature probe and Vital View computer software. This temperature was chosen as it represents "mild" hypothermia, and was thus thought to be clinically relevant, providing a good balance between side effects and benefit. After 90 minutes. . .

DETD Treatment with Xenon

DETD The same experimental paradigm was followed for treatment with xenon, but instead of hypothermia, the water bath was maintained at 37° C. and the gas mixture was changed to 25% oxygen and 75% xenon for 90 minutes. Gas was delivered into a purpose-built, closed system to minimise xenon leakage (FIG. 9). Once again, the pups were returned to their mothers until sacrifice.

DETD In the combination paradigm, the rats underwent both hypothermia and xenon concurrently for 90 minutes. Again, the pups were placed in airtight chambers, but on this occasion, their temperatures were maintained at 35° C. and the gas mixture consisted of 25% oxygen, only 20% xenon and balanced nitrogen. This temperature and xenon concentration was shown in preliminary experiments, to confer no neuroprotective benefit to the developing brain when used independently. Thus, by. . .

DETD . . . the combination group conferred no neuroprotection when used independently, two more groups of experimental rats were used: one group underwent hypothermia (as before) at 35° C., and the other group was exposed to xenon at a concentration of 20%.

DETD Xenon and Hypothermia as Independent Agents

DETD Xenon is Neuroprotective in the Neonate by an Anti-Apoptotic Mechanism

DETD Microscopic analysis of cortical and hippocampal brain regions demonstrated the neuroprotective properties of xenon, by the similar morphological appearance of xenon-treated brains as compared to sham brains, and the difference in appearance when compared to brains from rats that were not treated with xenon (FIG. 14). Profound neuroprotection against hypoxic-ischaemic injury in the neonatal rat was achieved by the use of xenon at its maximal concentration (75%), and this was quantified by histological analysis of brain slices stained with cresyl violet. The independent use of this concentration of xenon significantly decreased apoptotic cell death and increased the viable cell count. At 16 h, apoptosis in the cortex was reduced. . . The 24 and 48 h groups (FIGS. 15 and 16 respectively), showed similar results to the 16 h group, with xenon exhibiting statistically significant anti-apoptosis when compared to the positive control animals, in both the cortex and the gyrus.

DETD Anti-necrosis by xenon was shown to be statistically significant in the cortex at 48 h, where it decreased necrosis from 16.6%±0.2% in positive controls, to 10.7%±0.4% ($p<0.01$) (FIG. 16A). Xenon was not however anti-necrotic in the gyrus at 48 h (FIG. 16B). At all other time groups (16 and 24 h) xenon was not anti-necrotic.

DETD 90 Minutes of 33° c. Hypothermia after moderate HI is Ineffective

DETD No neuroprotection was observed with 33° C. hypothermia at 16 or 24 h (FIGS. 13 and 15 respectively). At 16 h, hypothermia appeared to have a significant anti-apoptotic effect in the cortex, but as the viable cell count was not statistically different to the positive control animals, it can be concluded that this intervention provided no neuroprotection. At 48 h however, hypothermia was neuroprotective via an anti-necrotic mechanism in the cortex, reducing the necrotic cell count from 16.6%±0.2% in the positive controls,. . . to 12%±2.3%, and increasing the viable cell count from 43%±3.4% to 52.3%±3.1% (FIG. 16A). In the gyrus at 48 h, hypothermia provided neuroprotection in an anti-apoptotic manner (FIG. 16B).

DETD Xenon and Hypothermia in Combination

DETD Treatment with 20% Xenon Alone Shows No Neuroprotection

DETD Contrary to the results obtained with 75% xenon, 20% xenon exerts no neuroprotective effect. By looking at FIG. 17, it can be seen that the percentage of apoptosis found in the cortex of the 20% xenon group at 16 h, is 36%±5.7% compared with 37%±2.5% in the positive control animals ($p>0.05$) and the percentage of viability. . .

DETD Treatment with 35° C. Hypothermia Alone Shows No Neuroprotection

DETD 35° C. hypothermia used alone is ineffective against HI, and shows no statistical difference in either brain area when compared to positive controls.. . .

DETD Treatment with a combination of 20% xenon+35° C. hypothermia demonstrates synergistic neuroprotection via an anti-apoptotic mechanism. By using proven ineffective interventions of either xenon (20%) or hypothermia (35° C.) in combination, a profound synergistic neuroprotection was demonstrated in both areas of the brain, and across all three. . .

DETD . . . the reduction of apoptosis due to the combination therapy, was found to be from 35.8%±5.7% and 47.6%±10.1% in the 20% xenon and 35° C. hypothermia groups respectively, to only 7.2%±2% in the combination group ($p<0.01$ and $p<0.001$ respectively), while the viable cells were increased from. . .

DETD . . . The level of neuroprotection provided by the combination of two individually ineffective interventions, demonstrates that synergy exists in vivo between xenon and hypothermia.

DETD . . .

Balduini, W., De Angelis, V., Mazzoni, E., Cimino, M., 2000. Long-lasting behavioural alterations following a hypoxic/ischemic brain injury in neonatal rats. Brain Research 859:318-325.

Bliss, T. V. P., Collingridge, G. L., 1993. A synaptic model of memory: long-term potentiation. . . M., Knight, R., Tidwell, C. D., Helpern, J. A., Brown, E., Welch, K. M., 1989. The metabolic effects of mild hypothermia on global cerebral ischemia and recirculation in the cat: comparison to normothermia and hypothermia. J Cereb Blood Flow Metab 9:141-148.

Chow, A., Ma, D., Hossain, M., Franks, N. P., Maze, M., 2003. Combined neuroprotection by xenon and hypothermia: Society Neuroscience Abstract 893(1).

Clancy, B., Darlington, R. B., Finlay, B. L., 2001. Translating developmental time across mammalian species. Neurosci 105(1):7-17.

Cullen, S. C., Gross, E. G., 1951. The anaesthetic properties of xenon in animals and human beings, with additional observations on krypton. Science 113:580-581.

Debillon, T., Daoud, P., Durand, P., Cantagrel,. . . (Eds), Basic

neurochemistry: Molecular, cellular and medical aspects, 6.sup.th edition, Lippincott-Raven, pp 316-333.
Eilers, H., Bickler, P. E., 1996. Hypothermia and Isoflurane similarly inhibit glutamate release evoked by chemical anoxia in rat cortical brain slices. Anesthesiology 85:600-607.
Engelhard, K.,. . .
Franks, N. P., Dickinson, R., de Sousa, S. L. M., Hall, A. C., Lieb, W. R., 1998. How does xenon produce anaesthesia? Nature 396(6709):324.
Goto, T., Nakata, Y., Morita, S., 2003. Will xenon be a stranger or a friend? Anesthesiology 98:1-2.
Goto, T., Saito, H., Nakata, Y., Uezono, S., Ichinose, F., Morita, S., 1997. Emergence times from xenon anaesthesia are: independent of the duration of anaesthesia. British Journal of Anaesthesia 79:595-599.
Graham, S. H., Shiraishi, K., Panter,. . . MacManus, J. P., Rasquinha, I., Tuor, U. I., 1995. DNA fragmentation indicative of apoptosis following unilateral cerebral hypoxia-ischemia in the neonatal rat. Brain Res 676:398-403.
Homi, H. M., Yokoo, N., Ma, D., Warner, D. S., Franks, N. P., Maze, M., Grocott, H. P., 2003. The neuroprotective effect of xenon administration during transient middle cerebral artery occlusion in mice. Anesthesiology 99:876-881.
Ikeda, M., Nakazawa, T., Abe, K., Kaneko, T.,. . . Neurotransmitters and apoptosis in the developing brain. Biochemical Pharmacology 62:401-405.
Ikonomidou, C., Mosinger, J. L., Olney, J. W., 1989. Hypothermia enhances protective effect of MK-801 against hypoxic/ischemic brain damage in infant rats. Brain Research 487:184-187.
Ikonomidou, C., Mosinger, J.. . . 36(1):82-90.
Ma, D., Wilhelm, S., Maze, M., Franks, N. P., 2002. Neuroprotective and neurotoxic properties of the `inert` gas, xenon. British Journal of Anaesthesia 89:739-746.
MacDonald, J. F., Schneiderman, J. H., Miljkovic, Z., 1986. Excitatory amino acids and regenerative. . . hypoxic ischemia in the newborn rat. J Neurosci 20(2):7994-8004.
Nakata, Y., Goto, T., Morito, S., 2001. Clinical pharmacology of xenon . Int Anesthiol Clin 39:63-75.
Nicholls, D. G., Budd, S. L., 2000. Mithochondria and neuronal survival. Physiol Rev 80:315-360.
. . . F. J., Ferriero, D. M., Graham, E. M., Traystman, R. J., Martin, L. J., 2001. Early neurodegeneration after hypoxia-ischemia in neonatal rat is necrosis while delayed neuronal death is apoptosis. Neurobiology of Disease 8:207-219.
Olney, J. W., 2003. Excitotoxicity, apoptosis. . . antagonist neurotoxicity: mechanism and prevention. Science 254:1515-1518.
Onitsuka, M., Satoshi, M., Inokuchi, H., Shigemori, M., Higashi, H., 1998. Mild hypothermia protects rat hippocarnpal CA1 neurons from irreversible membrane dysfunction induced by experimental ischemia. Neuroscience Research 30:1-6.
Pellegrino-Giampietro, D. E.,. . . may cooperate in the genesis of ischemia-induced damage. J. Neurosci 10:1035-1041.
Perlman, J. M., 1999. Markers of asphyxia and neonatal brain injury. NEJM 341 (5):364-365.
Petzelt, C., Blom, P., Schmehl, W., Muller, J., Kox, W. J., 2003. Prevention of neurotoxicity in hypoxic cortical neurons by the noble gas xenon. Life Sciences 72:1909-1918.
Pohl, D., Bittigau, P., Ishimaru, M. J., 1999. N-methyl-D-aspartate antagonists and apoptotic cell death triggered by. . . trauma in developing rat brain. Proc Natl Acad Sci 96:2508.
Reinelt, H., Marx, T., Schirmer, U., Schmidt, M., 2001. Xenon expenditure and nitrogen accumulation in closed-circuit anaesthesia.

Anaesthesia 56(4):309-311.
Riccio, A., Ginty, D. D., 2002. Nature Neurosci 5(5):389-390.
. . . and the pathophysiology of hypoxic-ischemic brain damage. Ann Neurol 19:105-111.
Sanders, R. D., Franks, N. P., Maze, M., 2003. Xenon: no stranger to anaesthesia. BJA 91(5):709-717.
Sattler, R., Xiong, Z., Lu, W., MacDonald, J. F., Tymianski, M., 2000. Distinct. . . Neurosci 20(1):22-33.
Shichino, T., Murakawa, M., Adachi, T., Miyazaki, Y., Segawa, H., Fukuda, K., Mori, K., 2002. Effects of xenon on acetlycholine release in the rat cerebral cortex in vivo. British Journal of Anaesthesia 88(6):866-868.
Talbot, J. H., 1941. The physiologic and therapeutic effects of hypothermia. N Eng J Med 224:281.
Taylor, D. L., Mehmet, H., Cady, E. B., Edwards, A. D., 2002. Improved neuroprotection with hypothermia delayed by 6 hours following cerebral hypoxia-ischemia in the 14-day-old rat. Ped Res 51(1):13-19.
Towfighi, J., Housman, C., Heitjan,. . . perinatal hypoxic-ischemic brain damage. Acta Neuropathol (Berl.) 87:598-604.
Treschera, W. H., Ishiwac, S., Johnston, M. V., 1997. Brief post-hypoxic-ischemic hypothermia markedly delays neonatal brain injury. Brain and Development 19:326-338.
Vannucci, R. C., 1997. Hypoxia-ischemia: Clinical Aspects in: Fanaroff, A. A., Martin, R. J., (Eds), Neonatal-perinatal medicine IV, Mosby-Yearbook Inc, Philadelphia, pp 877-891.
Vannucci, R. C., Connor, J. R., Mauger, D. T., Palmer, C., Smith,. . . and Developmental Disabilities Research Reviews 7: 56-64.
Wilhelm, S., Ma, D., Maze, M., Franks, N. P., 2002. Effects of xenon on in vitro and in vivo models of neuronal injury. Anesthesiology 96:1485-1491.
Wyllie, A. H., Kerr, J. F. R.,. . . at Birth. Scientific American October; 221(4):76-84.
Xu, L., Yenari, M. A., Steinberg, G. K., Giffard, R. G., 2002. Mild hypothermia reduces apoptosis of mouse neurons in vitro early in the cascade. J Cereb Blood Flow Metab 22:21-28.
Yager, J. Y., Asselin, J., 1996. Effect of mild hypothermia on cerebral energy metabolism during the evolution of hypoxic-ischemic brain damage in the immature rat. Stroke 27:919-926.

CLM What is claimed is:

1. Use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia in a neonatal subject, wherein said medicament is for use in combination with hypothermia.

20. A method of treating neonatal asphyxia in a mammal in need thereof, said method comprising: (a) administering a therapeutically effective amount of xenon to the mammal; and (b) subjecting the mammal to hypothermia.

22. A method according to claim 20 wherein the xenon is administered in combination with a pharmaceutically acceptable carrier, diluent or excipient.

23. A method according to claim 20 wherein the xenon is administered by inhalation.

24. A method according to claim 23 wherein the xenon is administered in the form of a 20 to 70% v/v xenon/air mixture.

25. A method according to claim 20 wherein the xenon is

administered by perfusion.

26. A method according to claim 20 to 22 wherein the xenon is administered in the form of a solution or emulsion.

27. A method according to claim 26 wherein the xenon is administered in the form of a lipid emulsion.

28. A method according to claim 26 wherein the xenon is administered intravenously, neuraxially or transdermally.

29. A method according to claim 20 wherein the xenon is administered simultaneously, sequentially or separately with hypothermia.

30. A method according to claim 29 wherein the xenon is administered simultaneously with hypothermia.

33. A method according to claim 20 wherein the hypothermia is maintained for a period of at least 6 hours after the hypoxic-ischemic (HI) insult.

34. A method according to claim 20 wherein the hypothermia is maintained for a period of from about 6 to about 24 hours after the hypoxic-ischemic (HI) insult.

35. A method according to claim 20 wherein the xenon is administered to the mother of the mammal prior to birth.

36. A method according to claim 35 wherein the xenon is administered to the mother of the mammal prior to, or during, labour.

37. A method according to claim 35 wherein the xenon is administered to the mother of the mammal for up to about 24 hours prior to birth.

38. A method according to claim 20 wherein the xenon is administered in a therapeutically effective amount.

39. A method according to claim 20 wherein the xenon is administered in a sub-therapeutically effective amount.

40. A method according to claim 20 wherein the xenon is administered in a combination with an aesthetic selected from isoflurane, sevoflurane and desflurane.

41. A method of treating neonatal asphyxia in a mammal in need thereof, said method comprising administering a therapeutically effective amount of xenon to the mammal in combination with hypothermia.

42. Use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia, wherein said treatment comprises administering to a subject simultaneously, sequentially or separately xenon in combination with hypothermia.

43. Use of xenon, in combination with hypothermia, for the treatment of neonatal asphyxia.

44. A method of treating neonatal asphyxia in a mammal in need

thereof, said method comprising: (a) administering a therapeutically effective amount of xenon to the mother of the mammal prior to and/or during labour; and (b) subjecting the mammal to hypothermia after birth.

L13 ANSWER 2 OF 9 USPATFULL on STN

ACCESSION NUMBER:	2007:89538 USPATFULL Full-text		
TITLE:	Methods, compositions and articles of manufacture for enhancing survivability of cells, tissues, organs, and organisms		
INVENTOR(S):	Roth, Mark B., Seattle, WA, UNITED STATES Morrison, Mike, Seattle, WA, UNITED STATES Blackstone, Eric, Seattle, WA, UNITED STATES Miller, Dana, Seattle, WA, UNITED STATES		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2007078113	A1	20070405
APPLICATION INFO.:	US 2006-408734	A1	20060420 (11)
	NUMBER	DATE	
PRIORITY INFORMATION:	US 2005-673037P	20050420 (60)	
	US 2005-673295P	20050420 (60)	
	US 2005-713073P	20050831 (60)	
	US 2005-731549P	20051028 (60)	
	US 2006-762462P	20060126 (60)	
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	FULBRIGHT & JAWORSKI L.L.P., 600 CONGRESS AVE., SUITE 2400, AUSTIN, TX, 78701, US		
NUMBER OF CLAIMS:	44		
EXEMPLARY CLAIM:	1-156		
NUMBER OF DRAWINGS:	40 Drawing Page(s)		
LINE COUNT:	9287		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . there are also therapeutic methods and apparatuses for organ transplantation, hyperthermia, wound healing, hemorrhagic shock, cardioplegia for bypass surgery, neurodegeneration, hypothermia , and cancer using the active compounds described.

SUMM Compositions and methods that do not rely fully or at all on hypothermia and/or oxygen may be useful in the context of organ preservation, as well as for tissue or cell preservation. Cells and tissue are currently preserved using hypothermia, frequently at temperatures substantially below freezing, such as in liquid nitrogen. However, dependence on temperature can be problematic, as apparatuses. . .

SUMM . . . the lack of ability to control cellular and physiologic metabolism in whole organisms subjected to traumas such as amputation and hypothermia is a key shortcoming in the medical field. On the other hand, the anecdotal evidence discussed above strongly suggests that. . .

SUMM . . . more, or any range derivable therein may be observed in methods of the invention. In some embodiments of the invention, hypothermia can be induced, such as moderate hypothermia (at least 10° F. reduction) or severe hypothermia (at least 20° F. reduction).

SUMM . . . result of cardiopulmonary bypass), or iii) as a result of blood loss due to trauma (e.g., hemorrhagic shock or surgery); hypothermia, where the biological material is subjected to

sub-physiological temperatures, due to exposure to cold environment or a state of low. . .

SUMM . . . a non-reactive gas in some embodiments. In some embodiments, the other gas is a noble gas (helium, neon, argon, krypton, xenon, radon, or ununoctium), nitrogen, nitrous oxide, hydrogen, or a mixture thereof. For instance, the non-reactive gas may simply be a. . .

SUMM . . . by employing oxygen antagonists or other active compounds. In some embodiments, there is a method of treating a subject with hypothermia comprising (a) contacting the subject with an effective amount of an oxygen antagonist, and then (b) subjecting the subject to. . .

SUMM . . . utilization in cells of the biological matter, reducing energy production derived from oxidative phosphorylation, and thereby decreasing thermogenesis, leading to hypothermia. Depending on the severity or time elapsed following the onset or progression of the injurious or disease insult, "stasis" may. . .

SUMM . . . limited to, the preparation of a medicament for the treatment of hemorrhagic or hematologic shock, wounds and tissue damage, hyperthermia, hypothermia, neurodegeneration, sepsis, cancer, and trauma. Moreover, the invention includes, but is not limited to, the preparation of a medicament for. . .

DRWD FIG. 15 Metabolic inhibition protects against hypothermia -induced death in Nematodes. Nematodes exposed to cold temperatures (4° C.) are unable to survive after 24 hours. However, if kept in anoxic conditions during the period of hypothermia (and for a 1 hour period before and after), a substantial proportion of the nematodes survive.

DETD While recovery has been reported from accidental hypothermia for a relatively prolonged period of time (Gilbert et al., 2000), there has been recent interest in intentionally inducing suspended. . .

DETD . . . worms survived with high viability after exposure to cold. Since carbon monoxide is a known stasis inducer in nematodes and neonatal human foreskin keratinocytes, the nematode assay is capable of identifying stasis inducing compounds as such by their ability to increase the survivability of worms exposed to lethal hypothermia when the worms are pre-equilibrated in the stasis inducer or other active compound.

DETD B. Hypothermia

DETD In yet another embodiment, the present inventor proposes use of the present invention to treat people with extreme hypothermia. The methods and compositions of the present invention are useful for inducing hypothermia in a mammal in need of hypothermia. Hypothermia can be mild, moderate or profound. Mild hypothermia comprises achievement of a core body temperature of approximately between 0.1 and 5 degrees Celsius below the normal core body. . . of the mammal. The normal core body temperature of a mammal is usually between 35 and 38 degrees Celsius. Moderate hypothermia comprises achievement of a core body temperature of approximately between 5 and 15 degrees Celsius below the normal core body temperature of the mammal. Profound hypothermia comprises achievement of a core body temperature of approximately between 15 and 37 degrees Celsius below the normal core body. . .

DETD Mild hypothermia is known in the art to be therapeutically useful and effective in both non-human mammals and in humans. The therapeutic benefit of mild hypothermia has been observed in human clinical trials in the context of out-of-hospital cardiac arrest. Exposure of humans to mild hypothermia in the context of cardiac arrest results in a survival advantage and an improved neurological outcome compared to standard of care with normothermia, or

absence of mild hypothermia (Bernard et al., 2002; The Hypothermia After Cardiac Arrest Study Group et al. 2002).

DETD . . . or surrounding the subject with a "cooling tent" that circulates cool air or liquid, for inducing mild, moderate, or profound hypothermia in mammals or humans. In these cases, the subject resists the reduction of core body temperature below normothermia and tries. . . heat by shivering. Shivering, and the body heat engendered therein, can have a negative impact on the achievement of mild hypothermia by, for example, slowing the rate of decrease in the core body temperature that is achieved using the standard methods of hypothermia induction. Consequently, humans subjected to therapeutic levels of hypothermia are also treated with a drug that inhibits shivering (by blocking neurotransmission at the neuromuscular junctions) (Bernard et al., 2002).

DETD . . . compositions of the present invention are combined with invasive methods or medical devices known in the art to induce therapeutic hypothermia in mammals or humans. Such invasive methods and devices include, but are not limited to, flexible probes or catheters that can be inserted into the vasculature of the subject in need of hypothermia, wherein the temperature of the catheter is adjusted to below the normal body temperature of the subject, resulting in the. . . modulated so as to maintain a pre-specified core body temperature. Such medical devices for achieving and maintaining mild or moderate hypothermia, referred to in the art as endovascular temperature therapy, are known in the art and are described for example on. . .

DETD The method provides that patients with extreme hypothermia are administered or exposed to an oxygen antagonist or other active compound and then gradually restored to normal temperature while. . .

DETD In one embodiment, a subject suffering from hypothermia with be given an oral or intravenous dose of an oxygen antagonist or other active compound. Intravenous provision may be. . .

DETD Recent studies suggest that transient and reversible lowering of the core body temperature, or "hypothermia," may lead to improvements in the fight against cancer. Hypothermia of 28° C. was recently found to reduce radiation, doxorubicin- and cisplatin-induced toxicity in mice. The cancer fighting activity of. . .

DETD . . . cooled and transported in cold storage. In the latter method, the following steps are typically employed: 1) pulsatile flow; 2) hypothermia; 3) membrane oxygenation, and 4) a perfusate containing both.

DETD Moreover, many, if not all, of the solutions and containers for organ preservation and transplantation involve hypothermia (temperature below room temperature, often near but not below 0° C.), which has been called the "bed rock of all. . .

DETD Moreover, many, if not all, of the solutions and containers for organ preservation and transplantation involve hypothermia (temperature below room temperature, often near but not below 0° C.), which has been called the "bed rock of all. . .

DETD . . . 49 78.7% ± 21.9 109
hif-1 (ia04) 0.0% ± 0.0 68 83.9% ± 13.8 108

Viability of Nematodes in Response to Hypothermia.

DETD . . . hr exposure to 4° C. (FIG. 15). In this experiment, the nematodes were kept in stasis during the period of hypothermia , and for one hour after they have been returned to room temperature. Anoxic conditions (pure N.sub.2), growth conditions, and viability. .

DETD Two identical experiments are planned under this protocol. Each

experiment will investigate the efficacy of H.sub.2S-induced hypothermia on the development of radiation induced lung injury. Ten mice per group will be exposed to one of four test. . .

DETD . . . Command. Walter Reed Army Institute of Research, Washington D.C., 1979.

Teodoro and OFarrell, EMBO J., 22(3):580-587, 2003.

The Hypothermia After Cardiac Arrest Study Group et al., 2002.

Tisherman, Crit. Care Med., 32(2):S46-S50, 2004.

Van Voorhies et al.,. . .

L13 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2007:299695 HCAPLUS Full-text

DOCUMENT NUMBER: 146:395071

TITLE: Asynchronous administration of xenon and hypothermia significantly reduces brain infarction in the neonatal rat

AUTHOR(S): Martin, J. L.; Ma, D.; Hossain, M.; Xu, J.; Sanders, R. D.; Franks, N. P.; Maze, M.

CORPORATE SOURCE: Department of Anaesthetics, Pain Medicine, and Intensive Care, The Blackett Laboratory, Imperial College London, London, SW7 2AZ, UK

SOURCE: British Journal of Anaesthesia (2007), 98(2), 236-240
CODEN: BJANAD; ISSN: 0007-0912

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Asynchronous administration of xenon and hypothermia significantly reduces brain infarction in the neonatal rat

AB Background: Neonatal asphyxia causes long-term neurol. and behavioral impairment in the developing brain. Concurrent administration of xenon and hypothermia synergistically reduces long-term damage in a rat model of neonatal asphyxia. This study sought to investigate whether asynchronous administration of xenon and hypothermia is capable of combining synergistically to provide neuroprotection. Methods. Seven-day-old rats were subjected to right common carotid artery occlusion followed by 90 min hypoxia with 8% oxygen. After a 1 h recovery period, rats received asynchronous administration of mild hypothermia (35°C) and xenon (20%) with a 1 or 5 h gap between interventions, xenon (20%) alone, or mild hypothermia (35°C) alone. Infarct volume in the brain was measured 4 days after injury. Results. Administration of hypothermia or xenon alone, 1 and 6 h after the hypoxic ischemic insult, resp., provided no neuroprotection. Asynchronous administration of xenon and hypothermia at a 1 h interval produced a significant reduction in infarct volume [93 (7) vs 74 (8); P<0.05]. Reduction in infarct volume was also present when hypothermia and xenon were asynchronously administered with an intervening gap of 5 h [97 (5) vs 83 (3); P<0.05]. Conclusions. This finding provides a rationale for investigating the combined use of hypothermia and xenon in a progressive manner for the management of neonatal asphyxia. Thus, hypothermia can be administrated at the site of delivery and xenon can be administered later.

ST xenon hypothermia brain infarction neuroprotectant neonate hypoxic ischemic injury

IT Asphyxia
Hypothermia
Ischemia
Newborn
(asynchronous xenon and hypothermia reduced brain infarction and combined synergistically to provide neuroprotection in rat model of neonatal hypoxic ischemia)

IT Brain, disease
(infarction; asynchronous xenon and hypothermia reduced brain infarction and combined synergistically to provide neuroprotection in rat model of neonatal hypoxic ischemia)

IT Cytoprotective agents
Nervous system agents
(neuroprotective agents; asynchronous xenon and hypothermia combined synergistically to provide neuroprotection in rat model of neonatal hypoxic ischemia)

IT Drug interactions
(synergistic; xenon and hypothermia in combination but not alone reduced brain infarction and synergistically reduced hypoxic ischemia injury in neonatal rat)

IT 7440-63-3, Xenon, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(asynchronous xenon and hypothermia reduced brain infarction and combined synergistically to provide neuroprotection in rat model of neonatal hypoxic ischemia)

L13 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:346872 HCAPLUS Full-text

DOCUMENT NUMBER: 142:386031

TITLE: Use of xenon with hypothermia for treating neonatal asphyxia

INVENTOR(S): Franks, Nicholas Peter; Maze, Mervyn

PATENT ASSIGNEE(S): Protexeon Limited, UK

SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005034966	A1	20050421	WO 2004-GB4298	20041011
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004280118	A1	20050421	AU 2004-280118	20041011
CA 2538104	A1	20050421	CA 2004-2538104	20041011
EP 1670489	A1	20060621	EP 2004-768829	20041011
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
BR 2004015232	A	20061212	BR 2004-15232	20041011
JP 2007508284	T	20070405	JP 2006-530602	20041011
US 2007104796	A1	20070510	US 2006-573093	20060323

PRIORITY APPLN. INFO.:	GB 2003-23861	A	20031010
	GB 2004-18539	A	20040819
	WO 2004-GB4298	W	20041011

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Use of xenon with hypothermia for treating neonatal asphyxia

AB The invention relates to the use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia in a neonatal subject, wherein said medicament is for use in combination with hypothermia.

ST xenon therapeutic hypothermia neuroprotectant neonatal asphyxia hypoxic ischemic stroke; inhalant xenon synergy hypothermia neonatal asphyxia hypoxia ischemia stroke; antiapoptotic mechanism neuroprotectant xenon synergy therapeutic hypothermia neonatal asphyxia

IT Drug delivery systems
(carriers; use of xenon with hypothermia for treating neonatal asphyxia)

IT Drug delivery systems
(inhalants; use of xenon with hypothermia for treating neonatal asphyxia)

IT Drug delivery systems
(injections, i.v.; use of xenon with hypothermia for treating neonatal asphyxia)

IT Emulsions
(lipid; use of xenon with hypothermia for treating neonatal asphyxia)

IT Drug delivery systems
(liqs.; use of xenon with hypothermia for treating neonatal asphyxia)

IT Asphyxia
(neonatal; use of xenon with hypothermia for treating neonatal asphyxia)

IT Drug delivery systems
(neuro-axial; use of xenon with hypothermia for treating neonatal asphyxia)

IT Cytoprotective agents
Nervous system agents
(neuroprotective agents; use of xenon with hypothermia for treating neonatal asphyxia)

IT Drug delivery systems
(perfusion; use of xenon with hypothermia for treating neonatal asphyxia)

IT Drug delivery systems
(solns.; use of xenon with hypothermia for treating neonatal asphyxia)

IT Brain, disease
(stroke, hypoxic-ischemic; use of xenon with hypothermia for treating neonatal asphyxia)

IT Drug interactions
(synergistic; use of xenon with hypothermia for treating neonatal asphyxia)

IT Drug delivery systems
(transdermal; use of xenon with hypothermia for treating neonatal asphyxia)

IT Anesthetics
Gases
Human
Hypothermia (therapeutic)
Hypoxia
Ischemia
Newborn
Parturition
Pregnancy

(use of xenon with hypothermia for treating neonatal asphyxia)

IT 7440-63-3, Xenon, biological studies
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of xenon with hypothermia for treating neonatal asphyxia)

IT 26675-46-7, Isoflurane 28523-86-6, Sevoflurane 57041-67-5, Desflurane
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of xenon with hypothermia for treating neonatal asphyxia)

L13 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2005:964377 HCAPLUS Full-text
DOCUMENT NUMBER: 143:416011
TITLE: Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia
AUTHOR(S): Ma, Daqing; Hossain, Mahmuda; Chow, Andre; Arshad, Mubarik; Battson, Renee M.; Sanders, Robert D.; Mehmet, Huseyin; Edwards, A. David; Franks, Nicholas P.; Maze, Mervyn
CORPORATE SOURCE: Departments of Anaesthetics and Intensive Care, Blackett Laboratory, Imperial College London, London, UK
SOURCE: Annals of Neurology (2005), 58(2), 182-193
CODEN: ANNED3; ISSN: 0364-5134
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia

AB Perinatal asphyxia can result in neuronal injury with long-term neurol. and behavioral consequences. Although hypothermia may provide some modest benefit, the intervention itself can produce adverse consequences. We have investigated whether xenon, an antagonist of the N-methyl-D-aspartate subtype of the glutamate receptor, can enhance the neuroprotection provided by mild hypothermia. Cultured neurons injured by oxygen-glucose deprivation were protected by combinations of interventions of xenon and hypothermia that, when administered alone, were not efficacious. A combination of xenon and hypothermia administered 4 h after hypoxic-ischemic injury in neonatal rats provided synergistic neuroprotection assessed by morphol. criteria, by hemispheric weight, and by functional neurol. studies up to 30 days after the injury. The protective mechanism of the combination, in both in vitro and in vivo models, involved an antiapoptotic action. If applied to humans, these data suggest that low (subanesthetic) concns. of xenon in combination with mild hypothermia may provide a safe and effective therapy for perinatal asphyxia.

ST neuroprotectant neonatal asphyxia xenon hypothermia hypoxic ischemic injury

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bax; combination therapy with xenon and hypothermia decreased apoptosis as evidenced by suppressed Bax expression causing neuroprotection from neonatal asphyxia after hypoxic-ischemic injury in brain of neonatal rat model)

IT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bcl-xL; combination therapy with xenon and hypothermia decreased apoptosis as evidenced by increased Bcl-xL expression causing neuroprotection from neonatal asphyxia after hypoxic-ischemic injury in brain of neonatal rat model)

IT Glutamate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NMDA-binding; glutamate receptor NMDA antagonist xenon with hypothermia showed synergistic neuroprotection from neonatal asphyxia in oxygen-glucose deprived neurons and in neonatal rat model after hypoxic-ischemic injury through antiapoptotic mechanism)

IT Asphyxia
(combination of xenon and hypothermia showed synergistic neuroprotection from neonatal asphyxia in oxygen-glucose deprived neurons and in neonatal rat model after hypoxic-ischemic injury through antiapoptotic mechanism)

IT Newborn
(combination of xenon and hypothermia significantly improved neurol. motor function, coordination and attenuated loss of brain matter than either agents alone in hypoxic-ischemic injured brain of neonatal rat model)

IT Apoptosis
(combination therapy with xenon and hypothermia decreased apoptosis as showed by increased Bcl-xL, suppressed Bax, caspase 3 expression causing neuroprotection from neonatal asphyxia after hypoxic-ischemic injury in brain of neonatal rat)

IT Necrosis
(combination therapy with xenon and hypothermia decreased necrosis in hypoxic-ischemic injured brain of neonatal rat model but showed no effect in oxygen-glucose deprived co-cultured mouse neuronal-glial cell)

IT Neuroglia
Neuron
(combination therapy with xenon and hypothermia protected coculture of mouse neuronal-glial cell injured by oxygen-glucose deprivation)

IT Brain
Hypothermia (therapeutic)
(combination therapy with xenon and hypothermia protected coculture of mouse neuronal-glial cell injured by oxygen-glucose deprivation, showed synergistic neuroprotection from neonatal asphyxia after hypoxic-ischemic injury in neonatal rat)

IT Ischemia
(combination therapy with xenon and hypothermia showed synergistic neuroprotection from neonatal asphyxia after hypoxic-ischemic injury evident by improved neurol. function in brain of neonatal rat model)

IT Drug targets
(glutamate receptor NMDA antagonist xenon with hypothermia showed synergistic neuroprotection from neonatal asphyxia in oxygen-glucose deprived neurons and in neonatal rat model after hypoxic-ischemic injury through antiapoptotic mechanism)

IT Nerve, disease
(injury; combination therapy with xenon and hypothermia protected coculture of mouse neuronal-glial cell injured by oxygen-glucose deprivation, showed synergistic neuroprotection from neonatal asphyxia after hypoxic-ischemic injury in neonatal rat)

IT Injury
(neuronal; combination therapy with xenon and hypothermia protected coculture of mouse neuronal-glial cell injured by oxygen-glucose deprivation, showed synergistic neuroprotection from neonatal asphyxia after hypoxic-ischemic injury in neonatal rat)

IT Cytoprotective agents
Nervous system agents
(neuroprotective agents; combination therapy with xenon and hypothermia protected coculture of mouse neuronal-glial cell injured by oxygen-glucose deprivation, showed synergistic neuroprotection from neonatal asphyxia after hypoxic-ischemic injury in neonatal rat)

IT 169592-56-7, Caspase 3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(combination therapy with xenon and hypothermia decreased apoptosis as evidenced by suppressed caspase 3 expression causing neuroprotection from neonatal asphyxia after hypoxic-ischemic injury in brain of neonatal rat model)

IT 7440-63-3, Xenon, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy with xenon and hypothermia protected coculture of mouse neuronal-glial cell injured by oxygen-glucose deprivation, showed synergistic neuroprotection from neonatal asphyxia after hypoxic-ischemic injury in neonatal rat)

L13 ANSWER 6 OF 9 USPATFULL on STN

ACCESSION NUMBER:	2004:307970 USPATFULL Full-text
TITLE:	Treatment using dantrolene
INVENTOR(S):	Anderson, David M., Ashland, VA, UNITED STATES Cameransi, Benjamin G., JR., Georgetown, SC, UNITED STATES Conklin, Vincent M., Richmond, VA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004242646	A1	20041202
APPLICATION INFO.:	US 2004-788413	A1	20040301 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2002-170236, filed on 13 Jun 2002, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-451249P	20030304 (60)
	US 2004-539324P	20040128 (60)
	US 2001-300482P	20010623 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	WHITHAM, CURTIS & CHRISTOFFERSON, P.C., 11491 SUNSET HILLS ROAD, SUITE 340, RESTON, VA, 20190
NUMBER OF CLAIMS:	82
EXEMPLARY CLAIM:	1
LINE COUNT:	2210

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . conditions, mechanical or assisted ventilation, or an

inadequate concentration of oxygen (insufficient FiO.sub.2), may induce a state of hypoxia. Accidental hypothermia, such as that associated with exposure, may also induce hypoxia.

SUMM . . . most mammals exist and thrive, normally a very narrow temperature range (the interthreshold range), being auto-regulated chiefly by the hypothalamus. Hypothermia in humans is largely regarded as being a core body temperature of less than 36 degrees C. In humans, raising. . .

DETD . . . by some patients after anesthetics and operations utilizing extracorporeal circulation, such as CPB, or in case where induced hypotension or hypothermia is performed, are the result of a constellation of factors, with no one event or factor being singularly dominant as. . .

DETD . . . body temperature to the above is important. Altered states of temperature are easily induced by medical practitioners. Non-normothermic states of hypothermia can be readily induced under general anesthesia both intentionally, as in cardiopulmonary bypass, or unintentionally, where appropriate safeguards are not. . .

DETD [0123] A number of potential complications are associated with unintentional intraoperative hypothermia including altered clotting function with increased blood loss, increased frequency of infection and myocardial stress. As such, the routine practice. . .

DETD [0124] Little evidence exists today to show that intraoperative hypothermia improves outcome except in the instance of deep hypothermia for circulatory arrest while undergoing cardiopulmonary bypass. Complete circulatory arrest for periods of up to one hour at core temperatures. . . trials during CPB and have shown little, if any benefit to the patient. The issue of employing mild to moderate hypothermia during CPB as a neuroprotective technique is difficult to assess because it requires not only reducing core temperatures but rapid re-warming cycles that usually delivers hyperthermic blood to the cerebrospinal system, which may negate any potential benefit that hypothermia may have provided

DETD [0125] Mild to moderate hypothermia has been evaluated in a large prospective randomized trial as a potential therapeutic maneuver to treat patients with traumatic brain injury while in the Intensive Care Unit. In this study, no benefit was attributed to hypothermia and, in fact, elderly patients suffered a greater rate of complications when randomly assigned to the hypothermic group.

DETD [0131] The neuroprotective effect of dantrolene may be compared with that of xenon, an agent previously shown to be protective in this animal model. (Ma et al, Anesthesiology. 2003 March; 98(3):690-8) In this. . . 15 min prior to undergoing 60 min of CPB with the same gas mixture as Group 2; and (Group 4) CPB+xenon rats undergo 60 min of CPB using an oxygenator receiving 30% O2, 60% xenon, 5% N2, and 5% CO2. Following CPB, the rats would recover for 12 days, during which they would undergo standardized neurologic and neurocognitive testing (Morris water maze). In this investigation, the sham, CPB+dantrolene and CPB+xenon groups all would have significantly better neurologic outcome compared to the CPB group on postoperative days 1 and 3. Compared to the CPB group, the sham, CPB+dantrolene, and CPB+xenon groups would have better neurocognitive outcome on postoperative days 3 and 4. By the 12th day, the neurocognitive outcome would remain significantly better in the CPB+dantrolene and CPB+xenon groups compared to the CPB group. This investigation would show the efficacy of dantrolene (10.0 mg/kg) in attenuation of CPB-induced neurologic and neurocognitive dysfunction is comparable to xenon.

DETD . . . techniques such as deep hypothermic circulatory arrest allowing for complex reconstructive open heart procedures such as aortic arch

repair/replacement in neonatal, pediatric and adult patients where minimal blood flow (approximately 90% of normal) is generated. Neurologic complications are reportedly as high. . .

DETD [0137] The invention also applies in relation to non-normothermic temperatures resulting from induced hypothermia techniques utilized as a possible neuroprotective measure or as a function of deep circulatory arrest while on CPB as well as the re-warming periods and possible hyperthermic overcorrection, and hypothermia resulting from the poikilothermic nature of anesthetized patients, as well as episodic hyperthermia resulting from exogenous or endogenous influences, including. . .

CLM What is claimed is:

. . . wherein said surgical procedure is a technique involving deep hypothermic circulatory arrest allowing for complex reconstructive open heart procedures in neonatal, pediatric and adult patients where minimal blood flow of approximately 90% of normal is generated.

. . . 64 wherein the surgical procedure is selected from the group consisting of techniques allowing for reconstructive open heart procedures in neonatal, pediatric and adult patients where minimal blood flow (approximately 90% of normal) is generated.

L13 ANSWER 7 OF 9 USPATFULL on STN

ACCESSION NUMBER: 2004:253822 USPATFULL Full-text

TITLE: Methods for vaccine identification and compositions for vaccination comprising nucleic acid and/or polypeptide sequences of the herpesvirus family

INVENTOR(S): Sykes, Kathryn F., Dallas, TX, UNITED STATES
Hale, Katherine S., Dallas, TX, UNITED STATES
Johnston, Stephen A., Dallas, TX, UNITED STATES

PATENT ASSIGNEE(S): Board of Regents, The University of Texas System (U.S. corporation)
MacroGenics, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004197347	A1	20041007
APPLICATION INFO.:	US 2003-669161	A1	20030923 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	KR 2003-34306	20030529
	US 2002-412956P	20020923 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FULBRIGHT & JAWORSKI L.L.P., 600 CONGRESS AVE., SUITE 2400, AUSTIN, TX, 78701
NUMBER OF CLAIMS: 73
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Page(s)
LINE COUNT: 10524
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DRWD . . . blisters and swollen lymph nodes as 5, lesions and erythemia as 6, ulcers and gut poresis were scored as 7, hypothermia as 8, paralysis and neural infections as 10 and death or euthanasia as 20. The values were further modified depending. . .

DETD . . . including both herpes simplex virus 1 and 2 (HSV-1, HSV-2). The increasing prevalence of genital herpes and corresponding rise of neonatal infection and the implication of Epstein-Barr virus

(EBV or HHV-4) and Kaposi's sarcoma herpesvirus as cofactors in human cancers create. . .

DETD . . . (.sup.97Ru), samarium (.sup.153Sm), scandium (.sup.47Sc), selenium (.sup.75Se), strontium (.sup.85Sr), sulfur (.sup.35S), technetium (.sup.99Tc), titanium (.sup.44Ti), tin (.sup.113Sn, .sup.117Sn), tritium (.sup.3H), xenon (.sup.136Xe), ytterbium (.sup.179Yb, .sup.175Yb), yttrium (.sup.90Y), zinc (.sup.65Zn); positron emitting metals using various positron emission tomographies, and non-radioactive paramagnetic metal. . .

L13 ANSWER 8 OF 9 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:205464 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400205980
TITLE: Combined neuroprotection by xenon and hypothermia.
AUTHOR(S): Chow, A. [Reprint Author]; Ma, D. [Reprint Author]; Hossain, M. [Reprint Author]; Franks, N. P. [Reprint Author]; Maze, M. [Reprint Author]
CORPORATE SOURCE: Anaesthetics and Biological Sci., Imperial Col. London, London, UK
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 893.1. http://sfn.scholarone.com. e-file. Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DOCUMENT TYPE: Conference; (Meeting) Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Apr 2004 Last Updated on STN: 14 Apr 2004

TI Combined neuroprotection by xenon and hypothermia.

AB Background: Xenon is an anaesthetic gas that exhibits neuroprotective properties (1) by acting as an antagonist at the N-methyl-D-aspartate (NMDA) glutamatergic receptor (2). Mild hypothermia has also been shown to be neuroprotective. In the present study we investigated the neuroprotective effects of xenon combined with hypothermia in an in vitro model of neuronal injury.Method: A co-culture of neuronal-glial cells was prepared from embryonic and neonatal mouse cortices. The cultures were exposed to 75 minutes of combined oxygen and glucose deprivation (OGD) before being allowed to recover for 6 hours in normoxic conditions at 37degreeC. This created a reproducible model of neuronal injury. Xenon (12.5, 25, 50, 75%), hypothermia (37-10degreeC), or a combination of these two interventions was applied during OGD and recovery. Neuronal damage was assessed by measuring lactate dehydrogenase(LDH) activity in the cell culture media following recovery.Results: Both xenon and hypothermia reduced LDH release induced by OGD in a concentration-and temperature-dependent manner. In combination, a temperature of 33degreeC reduced xenon 's ED50 to a concentration which was significantly lower ($p< 0.05$) than the predicted ED50 value assuming that the combined effect was simply additive. Similarly the presence of 12.5% xenon changed the ED50 of hypothermia to a temperature which was significantly higher ($p<0.05$) than the predicted ED50 value based upon simple additivity. Conclusions: Our data indicate that both xenon and hypothermia alone exert neuroprotective effects which acts in a synergistic manner when used in combination. Use of Xenon when combined with mild hypothermia may provide a greater degree of neuroprotection when used clinical setting. References: 1. Wilhelm S, et al.,Anesthesiology 2002;96:1485 2. Franks. . .

IT Major Concepts
Nervous System (Neural Coordination)
IT Parts, Structures, & Systems of Organisms

glial cells: nervous system
IT Diseases
hypothermia: disease-miscellaneous
Hypothermia (MeSH)
IT Diseases
neuronal injury: injury, nervous system disease
IT Chemicals & Biochemicals
LDH [lactate dehydrogenase]; NMDA [N-methyl-D-aspartate]; glucose; glutamatergic receptor; lactate; oxygen; xenon
RN 9001-60-9 (LDH)
9001-60-9 (lactate dehydrogenase)
6384-92-5 (NMDA)
6384-92-5 (N-methyl-D-aspartate)
50-99-7Q (glucose)
58367-01-4Q (glucose)
113-21-3 (lactate)
7782-44-7 (oxygen)
7440-63-3 (xenon)

L13 ANSWER 9 OF 9 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1993:144400 BIOSIS Full-text
DOCUMENT NUMBER: PREV199395077200
TITLE: Cerebral metabolism and circulatory arrest: Effects of duration and strategies for protection.
AUTHOR(S): Mault, James R. [Reprint author]; Ohtake, Shigeaki; Klingensmith, Mary E.; Heinle, Jeffrey S.; Greeley, William J.; Ungerleider, Ross M.
CORPORATE SOURCE: Duke Univ. Med. Cent., Box 3642, Durham, NC 27710, USA
SOURCE: Annals of Thoracic Surgery, (1993) Vol. 55, No. 1, pp. 57-64. ISSN: 0003-4975.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Mar 1993 Last Updated on STN: 16 Mar 1993

AB. . . C, and before and immediately after the experimental period at 18 degree C. Parameters measured included cerebral blood flow by xenon 133 clearance, arterial and sagittal sinus blood gases, and cerebral metabolism. Hypothermic total circulatory arrest caused an impairment of cerebral. . . was packed in ice. If technically feasible, CPB flow of only 5 to 10 mL cntdot kg-1 cntdot min-1 during hypothermia is superior to CA with respect to cerebral protection. Future studies with this model can be used to develop optimal modes of cerebral protection during neonatal heart operations.

IT Miscellaneous Descriptors
CEREBRAL BLOOD FLOW; CONGENITAL HEART DEFECTS; HYPOTHERMIA

=> s l11 and asphyxia
L14 8 L11 AND ASPHYXIA

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15 4 DUP REM L14 (4 DUPLICATES REMOVED)

=> d l15 1-4 ibib

L15 ANSWER 1 OF 4 USPATFULL on STN
ACCESSION NUMBER: 2007:120595 USPATFULL Full-text
TITLE: Use of xenon with hypothermia for

treating neonatal asphyxia
INVENTOR(S): Franks, Nicholas Peter, Highbury, UNITED KINGDOM
Maze, Mervyn, London, UNITED KINGDOM
PATENT ASSIGNEE(S): PROTEXEON LIMITED, London, UNITED KINGDOM, WC2B 4HN (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2007104796	A1	20070510	
APPLICATION INFO.:	US 2004-573093	A1	20041011	(10)
	WO 2004-GB4298		20041011	
			20060323	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2003-23861	20031010
	GB 2004-18539	20040819

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FAY SHARPE LLP, 1100 SUPERIOR AVENUE, SEVENTH FLOOR, CLEVELAND, OH, 44114, US
NUMBER OF CLAIMS: 45
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Page(s)
LINE COUNT: 1521

L15 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2007:299695 HCAPLUS Full-text
DOCUMENT NUMBER: 146:395071
TITLE: Asynchronous administration of xenon and hypothermia significantly reduces brain infarction in the neonatal rat
AUTHOR(S): Martin, J. L.; Ma, D.; Hossain, M.; Xu, J.; Sanders, R. D.; Franks, N. P.; Maze, M.
CORPORATE SOURCE: Department of Anaesthetics, Pain Medicine, and Intensive Care, The Blackett Laboratory, Imperial College London, London, SW7 2AZ, UK
SOURCE: British Journal of Anaesthesia (2007), 98(2), 236-240
CODEN: BJANAD; ISSN: 0007-0912
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:346872 HCAPLUS Full-text
DOCUMENT NUMBER: 142:386031
TITLE: Use of xenon with hypothermia for treating neonatal asphyxia
INVENTOR(S): Franks, Nicholas Peter; Maze, Mervyn
PATENT ASSIGNEE(S): Protexeon Limited, UK
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005034966	A1	20050421	WO 2004-GB4298	20041011
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004280118	A1	20050421	AU 2004-280118	20041011
CA 2538104	A1	20050421	CA 2004-2538104	20041011
EP 1670489	A1	20060621	EP 2004-768829	20041011
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
BR 2004015232	A	20061212	BR 2004-15232	20041011
JP 2007508284	T	20070405	JP 2006-530602	20041011
US 2007104796	A1	20070510	US 2006-573093	20060323

PRIORITY APPLN. INFO.:			
	GB 2003-23861	A	20031010
	GB 2004-18539	A	20040819
	WO 2004-GB4298	W	20041011

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2005:964377 HCAPLUS Full-text
DOCUMENT NUMBER: 143:416011
TITLE: Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia
AUTHOR(S): Ma, Daqing; Hossain, Mahmuda; Chow, Andre; Arshad, Mubarik; Battson, Renee M.; Sanders, Robert D.; Mehmet, Huseyin; Edwards, A. David; Franks, Nicholas P.; Maze, Mervyn
CORPORATE SOURCE: Departments of Anaesthetics and Intensive Care, Blackett Laboratory, Imperial College London, London, UK
SOURCE: Annals of Neurology (2005), 58(2), 182-193
CODEN: ANNED3; ISSN: 0364-5134
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his full

(FILE 'HOME' ENTERED AT 12:59:59 ON 17 MAY 2007)

FILE 'HCAPLUS, USPATFULL, BIOSIS, MEDLINE' ENTERED AT 13:00:07 ON 17 MAY 2007

L1 4167 SEA FLUDROCORTISONE OR FLORINEF
L2 59 SEA L1 AND COCHLEAR
L3 59 DUP REM L2 (0 DUPLICATES REMOVED)
L4 57 SEA L3 AND PREDNISONE
L5 57 SEA L4 AND (FLUDROCORTISONE (P) PREDNISONE)
D L5 40-57 IBIB KWIC

- Search History will be lost after eight hours of inactivity.
- Search numbers may not be continuous; all searches are represented.
- To save search indefinitely, click query # and select Save in My NCBI.
- To combine searches use #search, e.g., #2 AND #3 or click query # for more options.

Search	Most Recent Queries	Time	Result
#4	Search **#1 and #3**	14:48:30	15
#6	Search **#4 and #2**	14:48:21	2
#3	Search **asphyxia**	14:47:03	12882
#2	Search **hypothermia**	14:46:57	28828
#1	Search **xenon**	14:46:50	8791

Clear History

Day : Thursday
Date: 5/17/2007

Time: 14:24:08

PALM INTRANET

Inventor Information for 10/573093

Inventor Name	City	State/Country
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